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(54) Title: A PROCESS FOR THE PREPARATION OF QUETIAPINE AND INTERMEDIATES THEREFOR

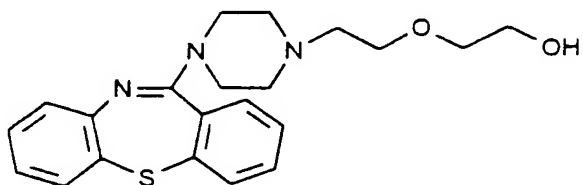
(57) Abstract: The invention refers to a novel process for the preparation of 11-[4-/2-(2-hydroxyethoxy)ethyl/-1-piper-  
azinyl]dibenzo[b,f]-1,4-thiazepine of the formula (I) known as quetiapine. According to the invention, a haloethylpiperazinylthi-  
azepine derivative of the formula (VIII), wherein Hal stands for a halo atom, is reacted with ethylene glycol.

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## A PROCESS FOR THE PREPARATION OF QUETIAPINE AND INTERMEDIATES THEREFOR

### Field of the invention

The invention refers to a novel process for the preparation of 11-[4-/2-(2-hydroxyethoxy)ethyl/-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine of the formula



known under the international non-proprietary name quetiapine. The compound has antidopaminerg and/or serotonin receptor antagonist activity, and is used in the clinical practice as an antipsychotic or neuroleptic.

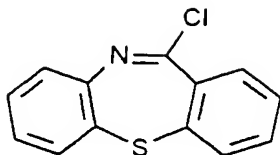
Furthermore, the invention refers to novel intermediates used in the novel process of the invention.

### Background of the invention

According to the process known from EP No. 240 228, the compound of the formula I is prepared by the reaction of the

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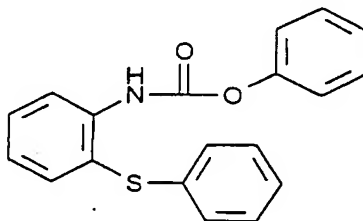
iminochloride of the formula



XI

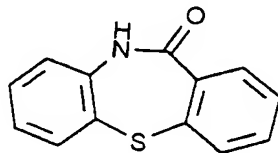
and 1-(2-hydroxyethoxy)ethylpiperazine. The oily crude product that forms is subjected to purification by chromatography using a silica gel column to obtain a yield of 77.7 % on a scale of about 0.5 moles.

The iminochloride of the formula XI used as the starting compound is prepared by the cyclization of the urethane derivative of the formula



IV

and halogenization of the formed dibenzo[b,f]-1,4-thiazepine-11(10H)-one of the formula



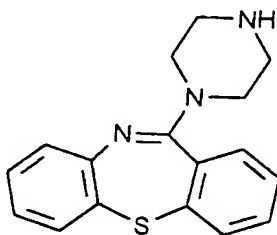
X

with phosphorus oxychloride according to the data of EP No. 282 236. The yield of the cyclization is 87 %, and that of the halogenization amounts to 92.6 %. Thus, in case of the above known process, the overall yield is 62.6 % calculated for the

urethane derivative of the formula IV.

Manufacture on an industrial scale using the known process is rendered difficult and extremely uneconomical, respectively, by the fact that a crystalline product of acceptable purity can be obtained only after purification by column chromatography. The iminochloride of the formula XI is rather unstable and hydrolyzes by the humidity of the air. When handling larger quantities, this side-reaction reduces the yield and the product of the hydrolysis contaminates the end-product. A further drawback resides in the fact that also the preparation of the 1-(2-hydroxyethoxy)ethylpiperazine can be carried out in several reaction steps which renders the known process still less economical.

According to the other process known from EP No. 282 236, the piperazine derivative of the formula



XII

is reacted with 2-haloethoxyethanol, and the product of the formula I is obtained in a yield of 78 %. The piperazine derivative of the formula XII is prepared by reacting the iminochloride of the formula XI with piperazine in a yield of 88 %, thus, the overall yield of the synthesis amounts to merely

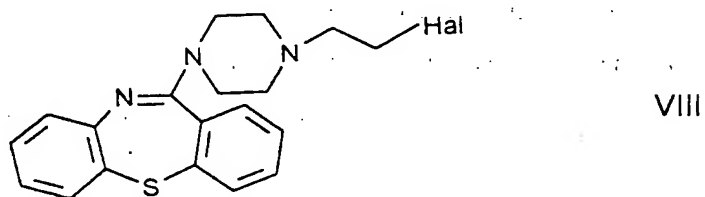
55.3 % calculated for the urethane derivative of the formula IV.

The aim of the invention is to provide an economical process for the preparation of quetiapine.

### Summary of the invention

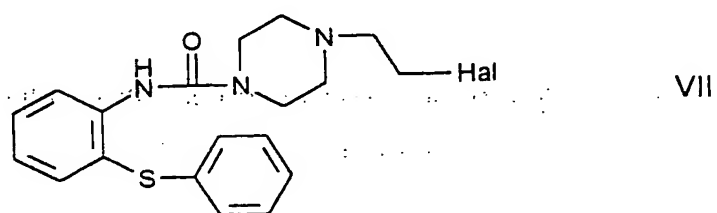
It has been found that the above aim is achieved in the process for the preparation of 11-[4-(2-(2-hydroxyethoxy)ethyl)-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine of the formula I or a pharmaceutically suitable acid addition salt thereof by

- a<sub>1</sub>) reacting a haloethylpiperazinylthiazepine derivative of the formula



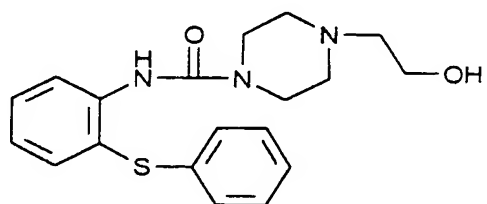
wherein Hal stands for a halo atom, with ethylene glycol; or

- a<sub>2</sub>) cyclizing a haloethylpiperazine derivative of the formula



wherein Hal represents a halo atom, in the presence of a dehydrating agent, and reacting the obtained haloethyl-piperazinythiazepine derivative of the formula VIII, wherein Hal is as defined above, with ethylene glycol; or

- a<sub>3</sub>) reacting the hydroxyethylpiperazine derivative of the formula



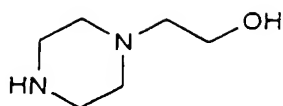
VI

with a halogenating agent, cyclizing the obtained haloethylpiperazine derivative of the formula VII, wherein Hal means a halo atom, in the presence of a dehydrating agent, and reacting the obtained haloethylpiperazinythiazepine derivative of the formula VIII, wherein Hal is as defined above, with ethylene glycol; or

- a<sub>4</sub>) reacting the hydroxyethylpiperazine derivative of the formula VI, simultaneously, with a halogenating agent and a dehydrating agent, and reacting the obtained haloethyl-piperazinythiazepine derivative of the formula VIII, wherein Hal stands for a halo atom, with ethylene glycol; or

- a<sub>5</sub>) reacting the urethane derivative of the formula IV with 1-(2-hydroxyethyl)piperazine of the formula

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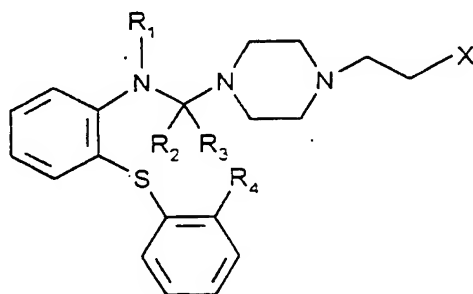


V

then reacting the formed hydroxyethylpiperazine derivative of the formula VI, simultaneously, with a halogenating agent and a dehydrating agent, and reacting the obtained haloethylpiperazinylthiazepine derivative of the formula VIII, wherein Hal represents a halo atom, with ethylene glycol;

and, if desired, converting the obtained product to an acid addition salt using a pharmaceutically suitable inorganic or organic acid.

Furthermore, the invention includes the novel piperazine derivatives of the formula



IX

wherein **either**

R<sub>1</sub> represents a hydrogen atom,  
 R<sub>2</sub> forms with R<sub>3</sub> an oxygen atom, and  
 R<sub>4</sub> stands for a hydrogen atom; **or**

R<sub>1</sub> forms with R<sub>2</sub> a valence bond between the adjacent

nitrogen and carbon atoms,  
R<sub>3</sub> forms with R<sub>4</sub> a valence bond between the adjacent  
carbon atoms, and  
X means a hydroxy group or a halo atom,  
and acid addition salts thereof formed with inorganic or organic  
acids.

The novel piperazine derivatives are intermediates in the novel  
process of the invention.

### **Description of the preferred embodiments**

In process a<sub>1</sub>) of the invention, the usual reaction terms of  
Williamson's synthesis are employed. At first, ethylene glycol is  
converted to alcoholate using sodium metal or any other  
suitable inorganic bases. In general, both sodium and ethylene  
glycol are used in excess; calculated for 1 mole of haloethyl-  
piperazinythiazepine derivative of the formula VIII, suitably 1.5-  
1.7 moles of sodium and 20-30 moles, preferably 25-27 moles  
of ethylene glycol are employed. The reaction temperature is  
mostly 50-150 °C, preferably about 100 °C. As a rule, the  
reaction proceeds in 5-15 hours, generally in about 9 hours.

In process a<sub>2</sub>) of the invention, the preferred starting compound  
is a haloethylpiperazine derivative of the formula VII, wherein  
Hal stands for a chloro atom, and the suitable dehydrating  
agent is phosphorus pentoxide. Suitably, also phosphorus  
oxychloride is added to the reaction mixture, and the ring



closure is carried out preferably at the boiling point of the reaction mixture. The haloethylpiperazinylothiazepine derivative of the formula VIII that forms is converted to the product of the formula I according to the method described in process a<sub>1</sub>).

In process a<sub>3</sub>) of the invention, suitably thionyl chloride or phosphorus oxychloride, preferably the latter, is used as the halogenating agent. The halogenation reaction is performed in an indifferent organic solvent or an excess of the halogenating agent can be used as the solvent, too. In general, halogenation is carried out at the boiling point of the reaction mixture. The haloethylpiperazine derivative of the formula VII that forms is converted to the product of the formula I according to the method described in process a<sub>2</sub>).

In process a<sub>4</sub>) of the invention, halogenation of the hydroxyethylpiperazine derivative of the formula VI and subsequent ring closure are carried out in one step without separating the haloethylpiperazine derivative of the formula VII that forms during the halogenation. Suitable halogenating agent is phosphorus oxychloride, preferred dehydrating agent is phosphorus pentoxide. An indifferent organic solvent can be added to the reaction mixture, or an excess of the halogenating agent is used as the solvent. Suitably, the reaction temperature is the boiling point of the reaction mixture. In most cases, the reaction time is 6-10 hours, preferably 7-8 hours. After the end of the reaction, the reaction mixture is poured onto water, made alkaline and extracted with a water-immiscible organic solvent

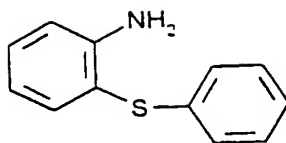
such as dichloromethane. Then, the procedure described in connection with process a<sub>1</sub>) of the invention is followed to prepare the product of the formula I.

In process a<sub>5</sub>) of the invention, the reaction of the urethane derivative of the formula IV with 1-(2-hydroxyethyl)piperazine is carried out in an indifferent organic solvent, generally an apolar organic solvent, preferably toluene. As a rule, the reaction temperature is higher than room temperature, preferably the boiling point of the solvent employed. The reaction time is relatively short, usually, the reaction proceeds completely in 2 hours. At first, the reaction mixture is washed with aqueous alkali, then with water to remove the phenol formed, the organic phase is dried and evaporated. The residue is crystallized from an organic solvent. The obtained hydroxyethylpiperazine derivative of the formula VI is converted to the product of the formula I by the method described in connection with process a<sub>4</sub>) of the invention.

The product of the formula I can be transformed into a pharmaceutically suitable acid addition salt in a manner known *per se*. Preferably, the hemifumarate is prepared. If desired, the base of the formula I can be liberated from the acid addition salt thereof in a manner known *per se*.

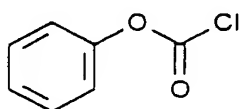
The urethane derivative of the formula IV can be prepared by a method known from the literature reacting the 2-amino-diphenyl sulfide of the formula

10



II

with phenyl chloroformate of the formula



III

The compound of the formula I is manufactured by the process of the invention in an overall yield of 66-67 % calculated for the urethane derivative of the formula IV. The reaction steps of the process of the invention can be performed easily, the starting compounds and reagents are readily available. The process of the invention does not comprise any procedure that would cause difficulties or would lower the yield. The quetiapine of the formula I that forms is of high purity.

The hydroxyethylpiperazine derivative of the formula VI, the haloethylpiperazine derivatives of the formula VII and the haloethylpiperazinylthiazepine derivatives of the formula VIII - all of which are intermediates in the process of the invention - are novel compounds.

The novel intermediates listed above are characterized by the formula IX. Thus, preferred representatives of the novel piperazine derivatives of the formula IX are the following compounds:

- the hydroxyethylpiperazine derivative of the formula VI and acid addition salts thereof;
- the haloethylpiperazine derivative of the formula VII, wherein Hal is as defined above, and acid addition salts thereof; and
- the haloethylpiperazinylothiazepine derivative of the formula VIII, wherein Hal is as defined above, and acid addition salts thereof.

An especially preferred haloethylpiperazine derivative of the formula VII is N-[4-(2-chloroethyl)piperazine-1-carbonyl]-2-aminodiphenyl sulfide and acid addition salts thereof.

An especially preferred haloethylpiperazinylothiazepine derivative of the formula VIII is 11-[4-(2-chloroethyl)piperazin-1-yl]-dibenzo[b,f]-1,4-thiazepine and acid addition salts thereof.

The novel intermediates can be prepared by the methods described above in connection with the process of the invention.

The invention is further elucidated by means of the following Examples.

**Preparation of the starting compound of the formula IV****Phenyl 2-phenylthiophenyl carbamate**

20.13 g (0.1 moles) of 2-aminodiphenyl sulfide are dissolved in 250 ml of dichloromethane, and the solution formed is cooled to 5 °C. Half of the solution of 18.79 g (15.1 ml, 0.12 moles) of phenyl chloroformate in 26 ml of dichloromethane are added, slowly, to the stirred solution of 2-aminodiphenyl sulfide, then, the other half of the solution of phenyl chloroformate as well as a solution of 3.0 g (0.075 moles) of sodium hydroxide and 9.2 g (0.0875 moles) of sodium carbonate in 50 ml of water are added, simultaneously, taking care that the inner temperature should not exceed 10 °C. After the end of the addition, the reaction mixture is stirred at room temperature for 3 hours, the organic phase is separated, washed three times with diluted hydrochloric acid using a total of 250 ml, dried over anhydrous magnesium sulfate, and evaporated. The residue is crystallized from n-hexane.

Thus, 29 g (90.2 %) of the title compound are obtained. M.p.: 90-91 °C.

Analysis: for  $C_{19}H_{15}NO_2S$  (321.401)

calculated: C 71.01 %, H 4.70 %, N 4.36 %, S 9.98 %;

found: C 71.19 %, H 4.69 %, N 4.33 %, S 9.84 %.

## Example 1

N-[4-(2-Hydroxyethyl)piperazine-1-carbonyl]-2-aminodiphenyl sulfide - the compound of the formula VI

32.1 g (0.1 moles) of phenyl 2-phenylthiophenyl carbamate are dissolved in 600 ml of toluene, and, to the stirred solution, 13.0 g (0.1 moles) of 1-(2-hydroxyethyl)piperazine are added. The reaction mixture is stirred at boiling temperature for 2 hours, then allowed to cool to room temperature, and washed with 600 ml of 1 N sodium hydroxide solution, then twice with 200 ml of water each time. The organic phase is dried over anhydrous magnesium sulfate, and evaporated. The residue is crystallized from a 10:1 mixture of n-hexane and ethyl acetate, filtered, washed with n-hexane, and dried.

Thus, 33.9 g (94.8 %) of the title compound are obtained in the form of white crystals. M.p.: 96-98 °C.

Analysis: for  $C_{19}H_{23}N_3O_2S$  (357.478)

calculated: C 63.84 %, H 6.49 %, N 11.75 %, S 8.97 %;

found: C 63.57 %, H 6.52 %, N 11.71 %, S 9.02 %.

## Example 2

N-[4-(2-Chloroethyl)piperazine-1-carbonyl]-2-aminodiphenyl sulfide - a compound of the formula VII

18.8 g (0.05 moles) of N-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-2-aminodiphenyl sulfide are boiled in 65 ml of thionyl chloride for 15 minutes, then evaporated, and the residue is

crystallized from n-hexane. 18.5 g (89.7 %) of product are obtained which is the hydrochloride of the title compound. M.p.: 180-183 °C.

**Formation of base:**

To a suspension of 10.31 g (0.025 moles) of the hydrochloride in 250 ml of isopropanol, 2.78 g (0.0275 moles) of triethyl amine are added, the reaction mixture is stirred at room temperature for 1 hour, poured onto water, extracted with dichloromethane, dried over anhydrous magnesium sulfate, and evaporated. Thus, 8.0 g (85.1 %) of the title compound are obtained.

**Formation of the salt with benzenesulfonic acid:**

To a solution of 7.5 g (0.02 moles) of the title base in 15 ml of ethanol, a solution of 3.48 g (0.022 moles) of benzenesulfonic acid in 10 ml of ethanol are added. The solution is stirred at room temperature for 1 hour, then cooled with ice water, filtered, and dried. Thus, 6.6 g (60.8 %) of product are obtained which is the benzenesulfonate of the title compound. M.p.: 110-112 °C.

Analysis: for  $C_{25}H_{28}ClN_3O_4S_2$  (534.101)

calculated: C 56.22%, H 5.28%, N 7.87%, Cl 6.64%, S 12.01%;

found: C 55.96%, H 5.35%, N 7.73%, Cl 6.50%, S 12.05%.

**Example 3**

11-[4-(2-Chloroethyl)-1-piperazinyl]-dibenzo[b,f]-1,4-thiazepine

- a compound of the formula VIII

## Method A)

A mixture of 8.2 g (0.02 moles) of N-[4-(2-chloroethyl)-piperazine-1-carbonyl]-2-aminodiphenyl sulfide hydrochloride, 84 ml of phosphorus oxychloride and 8.5 g (0.06 moles) of phosphorus pentoxide is reacted at boiling temperature for 15 hours. The solution is allowed to cool, then thoroughly evaporated, the residue is poured onto ice water, the solution is made alkaline by the addition of aqueous ammonia, and extracted with dichloromethane. The organic phase is evaporated, the residue is crystallized from diisopropyl ether, filtered, and dried.

Thus, 5.4 g (75.4 %) of the title compound are obtained. M.p.: 113-115 °C.

## Method B)

A mixture of 35.7 g (0.1 moles) of N-[4-(2-hydroxyethyl)-piperazine-1-carbonyl]-2-aminodiphenyl sulfide, 200 ml of phosphorus oxychloride and 31.2 g (0.22 moles) of phosphorus pentoxide is boiled for 7 hours. The solution is allowed to cool, evaporated, the residue is treated with ice water, made alkaline with aqueous ammonia, extracted with dichloromethane, dried over anhydrous magnesium sulfate, and evaporated again. The residue is crystallized from diisopropyl ether, the crystals are filtered and dried.

Thus, 28.6 g (80 %) of the title compound are obtained. M.p.: 114-116 °C.



Analysis: for  $C_{19}H_{20}ClN_3S$  (357.908)

calculated: C 63.76%, H 5.63%, N 11.74%, Cl 9.91%, S 8.96%;

found: C 63.70%, H 5.67%, N 11.68%, Cl 9.89%, S 9.07%.

#### Example 4

11-[4-/2-(2-Hydroxyethoxy)ethyl/-1-piperaziny]dibenzo[b,f]-1,4-thiazepine hemifumarate - the compound of the formula I

1.17 g of sodium metal are dissolved in 50 ml of ethylene glycol, and, to the solution obtained, a solution of 10.7 g (0.03 moles) of 11-[4-(2-chloroethyl)-1-piperaziny]-dibenzo[b,f]-1,4-thiazepine in 60 ml of toluene is added. The reaction mixture is stirred at 100 °C for 9 hours, then, after cooling, 210 ml of water are added. After separation, the toluene phase is extracted with diluted hydrochloric acid, the solution is made alkaline by the addition of aqueous ammonia, extracted with dichloromethane, the organic solution is dried over anhydrous magnesium sulfate, and evaporated under reduced pressure.

Thus, 11.27 g (98 %) of the title base are obtained.

#### Formation of salt:

10 g (0.026 moles) of the base obtained are dissolved in 130 ml of ethanol, and, to the solution, 3.13 g (0.027 moles) of fumaric acid are added. The mixture is stirred at boiling point for 25 minutes, then allowed to cool to room temperature. The mixture is maintained in a refrigerator for a night, then the crystals are filtered, washed with cold ethanol, and dried.

Thus, 9.8 g (85.4 %) of the title compound are obtained. M.p.:  
172-174 °C.

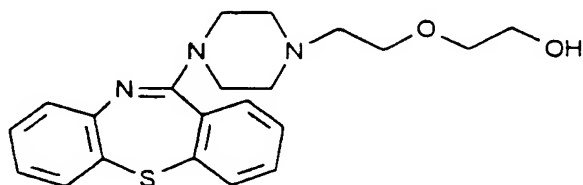
Analysis: for  $C_{46}H_{54}N_6O_8S_2$  (883.107)

calculated: C 62.56 %, H 6.16 %, N 9.52 %, S 7.26 %;

found: C 62.19 %, H 6.19 %, N 9.57 %, S 7.24 %.

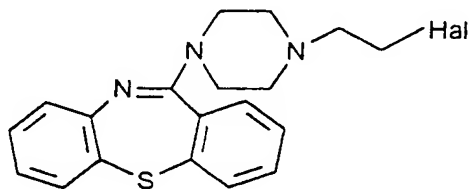
## Claims:

1. A process for the preparation of 11-[4-/2-(2-hydroxyethoxy)-ethyl/-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine of the formula



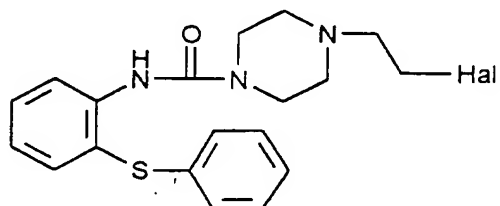
or a pharmaceutically suitable acid addition salt thereof,  
characterized by

- a<sub>1</sub>) reacting a haloethylpiperazinylthiazepine derivative of the  
formula



wherein Hal stands for a halo atom, with ethylene glycol; or

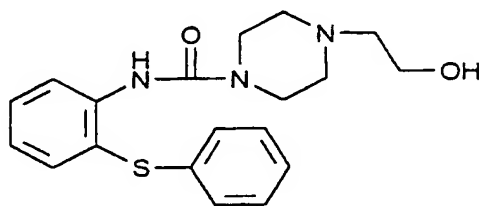
- a<sub>2</sub>) cyclizing a haloethylpiperazine derivative of the formula



wherein Hal represents a halo atom, in the presence of a

dehydrating agent, and reacting the obtained haloethyl-piperazinylthiazepine derivative of the formula VIII, wherein Hal is as defined above, with ethylene glycol; or

- a<sub>3</sub>) reacting the hydroxyethylpiperazine derivative of the formula

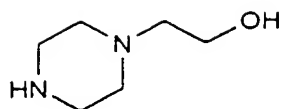


VI

with a halogenating agent, cyclizing the obtained haloethylpiperazine derivative of the formula VII, wherein Hal means a halo atom, in the presence of a dehydrating agent, and reacting the obtained haloethylpiperazinyl-thiazepine derivative of the formula VIII, wherein Hal is as defined above, with ethylene glycol; or

- a<sub>4</sub>) reacting the hydroxyethylpiperazine derivative of the formula VI, simultaneously, with a halogenating agent and a dehydrating agent, and reacting the obtained haloethyl-piperazinylthiazepine derivative of the formula VIII, wherein Hal stands for a halo atom, with ethylene glycol; or
- a<sub>5</sub>) reacting the urethane derivative of the formula IV with 1-(2-hydroxyethyl)piperazine of the formula

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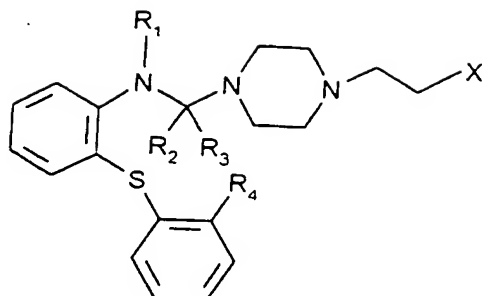
V

then reacting the formed hydroxyethylpiperazine derivative of the formula VI, simultaneously, with a halogenating agent and a dehydrating agent, and reacting the obtained haloethylpiperazinylthiazepine derivative of the formula VIII, wherein Hal represents a halo atom, with ethylene glycol;

and, if desired, converting the obtained product to an acid addition salt using a pharmaceutically suitable inorganic or organic acid.

2. A process as claimed in Claim 1 a<sub>1</sub>) in which the reaction is carried out in the presence of an inorganic base.
3. A process as claimed in Claim 1 a<sub>2</sub>) in which the starting compound is a haloalkylpiperazine derivative of the formula VII, wherein Hal stands for a chloro atom, and the dehydrating agent is phosphorus pentoxide.
4. A process as claimed in Claim 1 a<sub>3</sub>) in which the halogenating agent is phosphorus oxychloride.
5. A piperazine derivative of the formula

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IX

wherein **either**

R<sub>1</sub> represents a hydrogen atom,

R<sub>2</sub> forms with R<sub>3</sub> an oxygen atom, and

R<sub>4</sub> stands for a hydrogen atom; **or**

R<sub>1</sub> forms with R<sub>2</sub> a valence bond between the adjacent  
nitrogen and carbon atoms,

R<sub>3</sub> forms with R<sub>4</sub> a valence bond between the adjacent  
carbon atoms, and

X means a hydroxy group or a halo atom,

and acid addition salts thereof formed with inorganic or organic  
acids.

6. A hydroxyethylpiperazine derivative of the formula VI as  
claimed in Claim 5 and acid addition salts thereof.

7. A haloethylpiperazine derivative of the formula VII, wherein  
Hal stands for a halo atom, as claimed in Claim 5 and acid  
addition salts thereof.

8. A haloethylpiperazinylthiazepine derivative, wherein Hal  
stands for a halo atom, as claimed in Claim 5 and acid addition

salts thereof.

9. N-[4-(2-Chloroethyl)piperazin-1-carbonyl]-2-aminodiphenyl sulfide as claimed in Claim 7 and acid addition salts thereof.

10. 11-[4-(2-Chloroethyl)-1-piperaziny]dibenzo[b,f]-1,4-thiazepine as claimed in Claim 8 and acid addition salts thereof.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 01/00010

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D281/16 C07D295/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CH 422 793 A (WANDER AG DR A) 31 October 1966 (1966-10-31) page 5; example 42	5
X	CH 476 753 A (WANDER, A., A.-G.) 15 August 1969 (1969-08-15) column 11; example 42	5
X	US 3 539 573 A (HUNZIKER FRITZ ET AL) 10 November 1970 (1970-11-10) column 21; example 93	5
X	MCEVOY: J. MED. CHEM., vol. 13, 1970, page 295-297 XP000999698 page 295; figure I; example 4	1,3-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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- \*G\* document member of the same patent family

Date of the actual completion of the international search

18 May 2001

Date of mailing of the international search report

05/06/2001

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# INTERNATIONAL SEARCH REPORT

Int'l. Application No

PCT/HU 01/00010

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	ANDERSON ET AL.: ARZNEIM. FORSCH., vol. 12, 1962, pages 937-942, XP000999560 page 940; examples 40,42 ----	1,2,5,8, 10
Y	SCHMUTZ J: "IBER IN 11-STELLUNG AMINO-SUBSTITUIERTE DIBENZO(B,F)-1,4-THIAZAPINEUND -OXAZEPINE" HELVETICA CHIMICA ACTA,CH,VERLAG HELVETICA CHIMICA ACTA. BASEL, vol. 50, no. 1, 2 December 1966 (1966-12-02), pages 245-254, XP000560267 ISSN: 0018-019X page 246 ----	1
Y	JILEK ET AL.: COLLECT. CZECH. CHEM. COMMUN., vol. 48, no. 3, 1983, pages 906-927, XP000560351 page 918; example XA -----	1

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Information on patent family members

International Application No

PCT/HU 01/00010

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